Br J clin Pharmac 1993; **36**: 1–10

Do diuretics cause magnesium deficiency?

D. L. DAVIES & R. FRASER
Department of Medicine and Therapeutics and MRC Blood Pressure Unit, Western Infirmary, Glasgow

1 Controlled trials, of which there are few, do not substantiate claims that diuretics play a role in causing magnesium deficiency. Consequently, the vast majority of patients taking conventional doses of thiazide diuretics (i.e. bendrofluazide 2.5 mg day^{-1} or equivalent) do not need magnesium supplements. On balance, potassium-sparing diuretics tend to increase serum and intracellular magnesium content; this should not be taken as evidence of prior magnesium deficiency. It remains theoretically possible that large doses of loop diuretics given more than once daily for long periods could induce negative magnesium balance and magnesium deficiency. However, it has been difficult to run appropriately controlled trials in conditions where such therapy is needed (i.e. heart failure) and until more reliable information becomes available no absolute recommendation can be made.

2 Methods for the measurement of intracellular free magnesium levels are now available and are more relevant to the assessment of magnesium deficiency than total intracellular magnesium content; the complex relationship between intracellular free and total magnesium content remains to be defined. Future work involving the effect of diuretics on intracellular free magnesium measurements should make every attempt to avoid the errors of trial design and multiple publication that litter current and past literature.

Keywords magnesium diuretics review

Introduction

In this personal review, we have outlined the problems of detecting magnesium deficiency and have assessed the literature linking diuretics with magnesium metabolism with particular reference to the period 1985–1991. Earlier studies have been reviewed by Ramsay [1] and Swales [2].

Magnesium

Tissue levels and distribution

Body magnesium content (Mg_{TB}) in the adult is between 800 and 1200 mmol of which 60% is in bone, 20% in muscle and only 1% is extracellular [3, 4]. Most of this magnesium (Mg) has a very slow turnover rate. Principal dietary sources of Mg are green vegetables (Mg is a component of the chlorophyll molecule), nuts, fish, cereals and dairy products. Many factors affect absorption of Mg from the gut [5, 6] and the availability of internal Mg stores for redistribution [7]. Renal excretion can be reduced to as little as 1 mg day^{-1} in states of Mg deficiency, and Mg depletion by dietary means must be uncommon in subjects with normal intestinal and renal function.

Serum magnesium (Mg_S) concentration is usually maintained between 0.7 and 1.0 mmol l^{-1}. Like calcium, some of this Mg is non-specifically bound to protein (approximately 30%) with the remainder being mostly in the free ionized form. Clinically this distinction is often ignored.

Approximately 25% of filtered Mg is absorbed in the proximal convoluted tubule, 15% in the proximal straight tubule and 50% in the thick ascending limb of Henle's loop. Mg reabsorption within the loop may be affected by high serum Mg and calcium concentrations, perhaps due to inhibition of Mg transport at the basolateral membrane, and depends on both active and passive mechanisms [8, 9]. Factors said to increase Mg excretion are extracellular fluid volume expansion, hypermineralocorticoidism, renal vasodilation, loop and osmotic diuretics (probably through their effect on increasing flow rate into the loop and decreasing sodium chloride transport), metabolic acidosis and carbohydrate/protein/alcohol ingestion. PTH, calcitonin,

Correspondence: Dr D. L. Davies, University Department of Medicine and Therapeutics, Western Infirmary, Glasgow G11 6NT

ADH, glucagon (acting through cyclic AMP synthesis) and extracellular fluid depletion reduce Mg excretion. These hormone actions may be additive [8, 10].

Functions

Mg is a relatively small divalent cation which is a crucial co-factor in many enzyme reactions (e.g. glycolysis, cell respiration and membrane transport), particularly those involving the transfer of high-energy phosphate. Calcium, a larger ion, is present in much lower cellular concentrations, cannot fit into magnesium 'spaces' in enzymes and therefore cannot substitute for magnesium in these enzyme reactions [11]. Mg may alter intracellular calcium and hence vascular and myocardial contractility by inhibiting calcium influx, modulating second messenger systems or by competing with calcium for intracellular binding sites (see [12]). In addition, minor fluctuations in intracellular free magnesium $[Mg^{2+}]_i$ may have major effects on internal calcium ion concentration by altering (Ca^{2+})ATPase activity and the uptake of calcium ions across the sarcoplasmic reticulum [13]. Thus, Mg may act as a pharmacological agent and it should not be assumed that an observed clinical effect following Mg infusion reflects the correction of an underlying deficiency, i.e. magnesium may be beneficial in preventing cardiac arrhythmias, but this does not mean that magnesium deficiency exists or that Mg necessarily has a direct action on the heart [12, 14–20].

Factors controlling normal metabolism

Total plasma magnesium (Mg_P) concentration falls during situations associated with stress and following infusion of adrenaline, salbutamol, or insulin (for references see [21–25]). In the absence of net urinary loss, this presumably reflects movement of Mg into the cells. Similarly to potassium, exercise increases Mg_P acutely with post exercise concentrations falling below basal levels [26]. Aldosterone, thyroid hormone and free fatty acids have also been implicated in the regulation of Mg_S (27, 28]). Parathyroid hormone effects are difficult to assess in the presence of associated changes in calcium. Mg_S concentrations are normal in patients with parathyroid disease in contrast to intracellular magnesium status [29].

RBC uptake of ^{28}Mg both *in vitro* and *in vivo* is very slow [30, 31] even though $[Mg^{2+}]_i$ is at a level well below electrochemical equilibrium. Intracellular free magnesium is of the order 0.5 mmol l^{-1} (i.e. 0.5–5% total Mg; 11% for RBC) and varies within very narrow limits. It is very well buffered. Factors controlling change in $[Mg^{2+}]_i$ are not well known but plasma membranes are permeable to Mg albeit slowly, and an active $[Na^+]$–$[Mg^{2+}]$ exchanger to extrude Mg has been described in some cell types [13, 32–34]. Recent work in Mg-deplete cultured animal cells suggests that a specific and highly regulated Mg pathway, distinct from calcium, exists across the plasma membrane [35]; this is blocked by the calcium channel blocker verapamil. Epidermal growth factor increases ^{28}Mg uptake and $[Mg^{2+}]_i$ concentrations in mouse myocytes grown in culture. There seems to be a time lag between stimulus and effect similar to that noted for the stimulation of ^{28}Mg uptake by the diacylglycerol (DAG) mimic, phorbol ester, in lymphoma cells; the molecular mechanisms of the effect have been discussed by Grubbs [36]. A possible model for Mg transport involving efflux via activation of β-adrenergic receptors (and cAMP) and influx following muscarinic receptor activation (and DAG) has been suggested by Romani & Scarpa [37].

Assessment of magnesium status

'Recognition of Mg deficiency is problematic, since there is no test that will reliably and consistently detect the condition' [12]. Investigators have relied on measurements in serum or plasma, red or white blood cells, skeletal muscle, cardiac muscle or bone to assess Mg deficiency. Moreover, definition of deficiency has not been consistent.

Assay in blood and tissue

A variety of methods including titrimetric, fluorimetric, emission and absorption spectrophotometric and ion chromatographic techniques have been reported for the analysis of Mg_S [37, 38]. Most research workers now use atomic absorption spectrophotometry which is the reference method of choice; earlier reports may have used any of the techniques listed above. Many investigators have stressed the unsuitability of Mg_S as an assessment of body stores. Not all have taken the necessary precautions regarding patient (fasting, supine) and sample preparation (*viz* serum/plasma K) and serum protein correction. Others do not take into account the variability of magnesium estimations by replicating analysis and most of the reported trials relied on only a single Mg_S estimation. Kuller *et al.* [39] made a careful assessment of the variability of serum magnesium estimations (atomic absorption spectrophotometry) and found a substantial biological variation (coefficient of variation [CV] of 25%) between estimates taken 4 to 5 months apart. Technical errors were due to interfering ions (eliminated by using lanthanum diluent), instrument drift and inter-operator variation of up to 10%. Gonzalez-Revalderia *et al.* [40] reported a much smaller intra-individual variation (CV 3.4%) when weekly samples from the same individual were taken over 4 weeks, but these samples were analysed in the same batch. Obviously differences between samples taken 6 months to 6 years apart following diuretic therapy need to be critically assessed to take account of this type of error; quality control and a concurrent sample from an adequate control group would seem mandatory.

For white blood cells, intra-individual variations of 18.5 and 18.1% were obtained by Gallacher *et al.* [41] and Elin *et al.* [42] respectively (total magnesium content) when following subjects over a period of at least 20 weeks. The critical difference, i.e. that change required for two results from an individual to be significantly different ($P < 0.05$), is of the order of 54% and is much greater than the critical difference for red cells (18.6%).

This large intra-individual variation makes Mg_{WBC} less useful in following sequential changes in individual patients [41]. A lower variation (CV 8%) was noted by Sjogren *et al.* [43] but this related to samples taken over 5 consecutive days. Moreover, it is important to re-emphasise that there is little information in man to indicate whether Mg_{WBC} is representative of other tissues such as muscle, heart and bone [43–47].

Measuring $[Mg^{2+}]_i$ gives more directly relevant information about the influence of Mg on cellular processes than measurements of total cell Mg content. This is now possible and $[Mg^{2+}]_i$ has been measured in a variety of tissues by nuclear magnetic resonance, microelectrodes and ionophores [37, 48–50]. Ng *et al.* [51] have recently described a fluorimetric method based on the dye furaptra to measure $[Mg^{2+}]_i$ in human peripheral blood lymphocytes and showed that only 0.5% of lymphocyte Mg is in the unbound state. Repeated readings on the same sample of cells are possible.

Bound Mg can be measured by electron probe X-ray techniques and clearly gives additional information, for example on the status of energy metabolism since ATP is a Mg complex.

Magnesium loading test

The excretion of parenterally administered Mg has been used to assess Mg deficiency in man; 80% or more of an administered dose is usually excreted within 24 h [52]. Its use has been validated in adult rats fed low, intermediate and high Mg diets [53]. However, Mg excretion will also depend on renal function. The effect of diuretic therapy (or its withdrawal) on the validity of the test has not been critically assessed.

Total body magnesium

Only 23% of Mg_{TB} (15 mmol kg^{-1}) exchanges with administered Mg isotope after 120 h and most of this is in tissues other than muscle or bone [31, 54, 55]. Given the relatively large variation from subject to subject, the short half-life (21.4 h) of the radioactive isotope (^{28}Mg) and cost, routine clinical measurement of exchangeable Mg_{TB} is not yet feasible.

Effects of manipulating intake

Animals

In rats, dietary Mg restriction causes total Mg concentrations in plasma, erythrocytes, skeletal muscle and bone to fall with Mg_S falling more than intracellular Mg [4, 47, 56]. Intracellular magnesium stores in skeletal muscle (Mg_{SM}) are best protected from the effect of dietary restriction and this is more apparent following exercise [57]. Both muscle and plasma potassium concentrations fall with those of Mg and this can be corrected by restoring Mg to the diet [58]. The fall of 21% in Na,K pump sites ([^{3}H]-ouabain binding) in rat skeletal muscle may be secondary to potassium rather than magnesium depletion [59]. How the relationship between extracellular and intracellular free Mg changes during dietary restriction is unclear. In dogs, RBC $[Mg^{2+}]_i$ fell in parallel with serum levels [60]. In contrast, intracellular free $[Mg^{2+}]_i$ in guinea pig and ferret myocardium was unchanged despite falls in extracellular Mg concentration [61].

Man

In human subjects, Mg_S concentration does not always fall following dietary Mg restriction with resulting negative Mg balance [62–65]. Neurological signs have been noted (tremor, fasciculation, spasticity, carpopedal spasm) but hypocalcaemia and hypokalaemia are usually also present and so these signs are non-specific [4]. The hypocalcaemia may be secondary to impaired parathormone secretion brought about by Mg deficiency [66]. Whether negative Mg balance results in exchange between total and free intracellular Mg is uncertain [36, 67]. Low $[Mg^{2+}]_i$ can be achieved by growing cells in Mg deplete media and this inhibits glycolysis and protein biosynthesis. However, this degree of Mg deficiency is much more severe than that found clinically where $[Mg^{2+}]_i$ content is only slightly reduced [68]. Dietary Mg deficiency differs from diuretic-induced losses since the latter situation also causes decreased ECF volume, secondary changes in the renin/aldosterone system, and perhaps redistribution of Mg between ECF/ICF.

Diuretics

Animals

Micropuncture studies in hamsters have shown that thiazide diuretics have little effect on Mg reabsorption in the distal tubule [27]. However, frusemide and loop diuretics can cause large increases in magnesium excretion over 6 h [64, 69, 70]. Large doses may be needed. Borchgrevink *et al.* [71, 72] found it necessary to use large doses of oral loop diuretics, higher than those producing maximal natriuretic effect, coupled with dietary Mg restriction to 1/3 of recommended intake before Mg deficiency could be induced in rats. Wong *et al.* [47] used even larger (fourfold) doses of intraperitoneal frusemide for 19 weeks in rats on a normal magnesium intake. At the end of this period, Mg_S had fallen 9% and lymphocyte magnesium 48% compared with control rats; Mg_{SM} and Mg_{heart} were unchanged. Adam *et al.* [73] found no evidence of tissue or brain (but see [74]) Mg deficiency in chlorothiazide-fed rats whilst dietary Mg restriction did cause detectable tissue deficiency. Similarly, Rabkin & Roob [75] found that hydrochlorothiazide for 18 days slightly increased the Mg_{heart} content of male Wistar rats (13%, not significant) whilst reducing Mg_S concentration by 12.5% ($P < 0.05$). Diuretics do not affect Mg_{bone} content under normal dietary conditions [76 but see 47].

In many of these studies, amiloride has been shown to cause Mg retention. The somewhat variable results seen in experimental animals may result from differences in diet, dosage, age and species sensitivity to diuretic agents.

Man

Short-term diuretic administration is less likely to cause Mg deficiency than continuous use and so we have divided reports accordingly.

Single doses Single doses of diuretics increase urinary magnesium excretion (Mg_U) to a degree which depends on the amount and type of drug. However, excretion with loop diuretics tends to be acute, short-lived and followed by a compensatory decreased Mg_U, whereas thiazide type diuretics have a later and more prolonged effect. Whether total 24 h Mg_U after a single therapeutic dose is increased remains controversial. Earlier studies (see [1]) used large doses, collected urine for varying times post-dosing and were poorly controlled. However, in a series of double-blind, random order, placebo controlled studies, Reyes and colleagues [77–80] showed statistically significant increases over basal Mg_U for hydrochlorothiazide, chlorthalidone and frusemide. There was no evidence of a dose-response relationship and spontaneous variation from day to day was not assessed. Other workers have shown only small increases in Mg_U following single doses of frusemide [81, 82] and these did not reach statistical significance. Labeeuw *et al.* [83] using 2 mg methylclothiazide by mouth (placebo, random order) found Mg_U to be increased by only 14% whereas the average day to day spontaneous variation was 32% (range 11–60%). Interestingly, Kiil [84] using a random crossover study (advanced for the period) could show no difference in 24 h Mg_U following placebo, chlorothiazide or hydrochlorothiazide. However, there was no washout period and 'carry over' may have occurred.

Single doses of potassium-sparing diuretics such as amiloride or triamterene, alone or in combination with frusemide, have little effect on Mg_U [80, 85, 86].

The effect of a diuretic may vary, depending on whether subjects are water-loaded (enhancing), neutral or water-restricted. In general, thiazide diuretics seem to produce a variable mild magnesuria which may depend on the flow rate into the loop of Henle [8].

Up to 1 week of treatment Earlier studies in renal stone 'formers', normal and hypertensive subjects showed an initial increase in Mg_U (25–70%) following thiazide diuretics, generally falling to, or near, control values within 3 or 4 days [87–89]. However these studies were poorly controlled, being of a before and after type (B/A). Nevertheless, a random order, placebo-controlled study [83] confirmed the findings with an average total Mg_U loss during the first 4 days of methylclothiazide therapy of 0.62 mmol day^{-1} (15%) above placebo values; the maximal loss occurred on day 2.

Jorgensen & Transbol [87] noted a 10% fall in serum total and ultrafiltrable magnesium following 3–5 days of treatment with bendrofluazide 10 mg daily. In contrast, other studies (B/A) found no change in total Mg_S concentration following mefruside [90], trichlormethiazide [89] or hydrochlorothiazide [91]. Lipworth *et al.* [92] (placebo, crossover) could not detect changes in Mg_P concentration following 5 mg bendrofluazide daily for 7 days. Mg_{SM} concentration was similarly unaffected (B/A) following mefruside [90].

Potassium-sparing diuretics have a variable effect on plasma and cell Mg concentrations. In the double-blind crossover part of their trial, McInnes & Davies [91] did not detect any further change in Mg_P in normal subjects following the addition of 25 or 100 mg spironolactone to 100 mg hydrochlorothiazide daily but the addition of amiloride increased Mg_P concentration significantly in a dose-dependent manner. In contrast, amiloride failed to ameliorate the fall in Mg_{RBC} red cell magnesium following hydrochlorothiazide whereas spironolactone was effective. Total lymphocyte Mg concentration increased following the addition of amiloride (10 mg twice daily) to frusemide in heart failure [93]; Mg_{SM} concentration was not altered by amiloride (15 mg daily) combined with hydrochlorothiazide (50 mg daily) [94]. Triamterene opposes the initial mild magnesuria induced by thiazide diuretics but apparently only at low doses [83]. Therefore, at 1 week thiazide diuretics have caused little change in Mg_{TB} status apart from a mild magnesuria.

Up to 6 weeks treatment Pak [95] gave hydrochlorothiazide (50 mg twice daily) for 1 month to six renal stone formers who were evaluated in hospital beforehand and again after treatment on the same diet (equilibration period 3 days). Mg_U was not increased at one month. Goldenberg *et al.* [96] studied Mg_U when thiazides (see Table 1) were reintroduced for 1 month after discontinuing long-term diuretic therapy for 4 weeks. Again no increase in Mg_U could be demonstrated.

Results of controlled and semi-controlled studies are shown in Table 1. It can be seen that following thiazide or loop diuretic therapy, Mg_S or Mg_P concentration has been variously shown to fall by between 4.7 and 11% [97–100], to remain unchanged [96, 101] or to increase by up to 28% [102, 103]. Salivary magnesium secretion does not alter [104]. Mg_{WBC} was unchanged (B/A) following hydrochlorothiazide [105].

Mg_{RBC} content was unchanged in the studies of Kisters *et al.* [98], Sundberg *et al.* [101] and Zemel *et al.* [106] (presumed 4 week treatment periods comparing hydrochlorothiazide and hydrochlorothiazide with added triamterene) but Fehske *et al.* [103] found total Mg and $[Mg^{2+}]_i$ increased significantly following piretanide. Triamterene added to a thiazide diuretic produces a variable increase in Mg_{RBC} content [101, 106]. Overall, there is not much evidence of Mg deficiency at 6 weeks.

More than 6 weeks treatment Approximately 50 'trials' have been identified; only those having an 'adequate' control group are shown in Table 2. Dosage, type of diuretic drug and diagnostic grouping has varied considerably but it can be seen that change in Mg_S/Mg_P concentration following thiazide or loop diuretic can vary from falls of 10% to increases of 5.9%. Few of these changes reach statistical significance. Few studies include a placebo group and many in consequence reach unsupportable conclusions. The only studies involving the use of placebo tablets were those of Taylor *et al.* [107], McVeigh *et al.* [108], Laerum

Table 1 Diuretic studies of magnesium status and lasting less than 6 weeks in duration. Drug dosages in mg. The effect of a diuretic is represented either as a % change from baseline observations (i.e. a, b, c) or as a comparison between drugs ((a) *vs* (b))—see comments

Reference	*Type of study*	*Time (weeks)*	*Drug*	*Change in serum Mg (%)*	*Other 'tissue'*	*Diagnosis number of patients*	*Comments*
97	OPEN PG	4	a) Frumil b) Burinex K a *vs* b	0% −6%** −6%*		CCF 20 CCF 20	a, b, Compared with basal. 'n' changing through treatment. Burinex group more severe CCF? Elderly.
102	DB CO	2	a) HCH 50 b.d. b) Placebo a *vs* b	+5.6% +2.6% +3%		EH 20	a, b, Compared with basal. No change in exercise induced rise in serum Mg. No washout.
104	DB CO	2	a) Bendro 2.5 b) Placebo		No change Salivary Mg	Normal 34	2 week washout period.
98	B/A PG	4	a) TCL 4 b) TCL 2 +A2 a *vs* b	−8.5% +2.5% −7.7%	RBC +2% 0%	EH 14 EH 11	a, b, Compared with basal. RBC Mg significant fall at 8–12 weeks.
99	DB CO	4	a) HCh 50 b) HCh 100 c) HCh +A	−8.0% −11.8%** 0%		EH 10	No placebo. LD. Treatments separated by 4 week washout periods. Results compared with mean washout.
96	B/A	4	HCh 25/50	0%	RBC Membrane ATPase unchanged	EH 8	Long-term thiazide treatment stopped for 1 month and then restarted for 1 month. Serum magnesium +5% on long-term treatment.
101	DB CO	4	a) HCh 25 b) +A 2.5 c) +T 37.5	0% +1.3% 0%	Whole blood −1.8% +0.9% +3.6%	EH 11	No placebo. 3 week washout period. Results compared with preceding washout.
103	B/A	6	PR 6 mg		RBC +6.8%*	EH 18	Intracellular *free* Mg (RBC) +39% * (ion selective electrodes).

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.
A, amiloride; AMI, acute myocardial infarction; B, bendrofluazide; B/A, before and after; BB, β-adrenoceptor blocker; b.d., twice daily; Burinex K, bumetanide/potassium; CALC, renal stone formers; CCF, heart failure; CLT, chlorthalidone; CO, crossover; CYCLO, cyclopenthiazide; DB, double blind; EH, hypertension; ERC, efflux rate constant; F, frusemide; FRUMIL, frusemide and amiloride; HCh, hydrochlorothiazide; IC, intracellular; IHD, ischaemic heart disease; LD, limited data; M, months; MCLO, methylchlothiazide; MRT, magnesium retention test; P, placebo; PG, parallel groups; PR, piretanide; SB, single blind; SPIRO, spironolactone; TCL, trichlormethiazide; TRI, triamterene; VES, ectopic ventricular beats; W, weeks; XS, cross section population.

[109] and Siegel *et al.* [110]. No changes in Mg_S, Mg_{RBC} or Mg_{WBC} were noted.

Three studies of Mg_U revealed no clear pattern [109, 111, 112]. Mg retention following a Mg load (i.e. an index of magnesium deficiency) has been shown to be increased in two studies [113, 114] but only reached significance in the study of Cocco *et al.* [113]. Total intracellular magnesium concentration (red cell, white cell and skeletal muscle) may be reduced but again study design (see Table 2) can be criticised in some of these reports [111, 112, 115, 116]. In contrast, Mg_{WBC} was unchanged in patients with congestive cardiac failure taking a loop diuretic whilst $[Mg^{2+}]_i$ was increased 33% in those patients taking a potassium-retaining diuretic [117]. Again, the study was not properly controlled since normal subjects were compared with heart failure patients.

There are many other uncontrolled studies with conflicting results. Mg_P concentration may [118, 119] or may not [120] be related to duration of diuretic treatment; larger doses seem more likely to be associated with reports of hypomagnesaemia. Significant falls in Mg_{RBC} have been reported by Kisters *et al.* [98] and Petri *et al.* [121] whilst those reported by Abraham *et al.* [122], although large, did not reach statistically significant levels. In contrast, unchanged or increased Mg_{RBC} has been reported by Cohen *et al.* [123], Halawa [124], Seller *et al.* [125, 126], Ralston *et al.* [46] and Schwinger & Antoni [127]. Mg_{SM} was significantly decreased in some studies [128, 129] but normal or increased in others [90, 123, 130–133]. Interestingly, in the three of these studies in which the addition of a potassium-sparing diuretic to long-term thiazide diuretic therapy was compared with the continued use

Table 2 Diuretic studies of magnesium status and lasting more than 6 weeks in duration. Design and abbreviations as for Table 1.

Reference	*Type of study*	*Time (months)*	*Drug*	*Serum or plasma*	*RBC or WBC*	*Other*	*Diagnosis number of patients*	*Comments*
109	PC PG	10	a) HCh 25 b.d. b) Placebo	−10%		*Urine* −2.7%	Calc 23 Calc 25	Results compare P *vs* HCh at 10 months.
137	DB PG	5.5	a) HCh 50 b) HCh 50 + A 5	−9.1%* −9.7%*			EH 9 EH 12	No P. Results compared with basal. No difference between effect of trial drugs.
138	CO	2	a) CLT 25 b.d. b) A 10 b.d.	0		*ECG* increased VES	EH/IHD 10	No P. LD. Spiro and Cyclo used in some patients.
115	PG	6			*RBC*	*WBC*	AMI	Controls did not have CCF.
			a) F49 + KCl	LD	a) −4.8%*	a) −39%*	48	Results compare (a) *vs* (c), (b) *vs* (c). Group (a) lower RBC at start.
			b) HCh 50 + A 5	No change	b) −1.2%	b) −4.5%	37	
			c) Control				70	
139	DB PG	3	a) PR 3–12 b) TRI 50 b.d. c) HCh 50 + A 5 b.d.	−1 to +3.3% +4.3% 0%			EH 188	Re-analysis of 4 earlier studies. No P. Results compared with baseline.
113	SB PG	12				*MRT*		No. P. Results compared with basal. Various doses BB and CLT. Also assessed at 6 months. Relation of diuretics to MRT not stated.
			a) BB	a) −13%		a) +12.6%	EH 30	
			b) BB+ CLT 12.5/50	b) −5.5%		b) +301%*	EH 30	
111	XS	53	a) TCL 2–4 *or* MCLO 2.5/5	−3.4%	*RBC* −34%*	*Urine* +20%	EH 20	Controls matched age/sex/BP. RBC Mg method CV = 13% interassay. Sodium ERC (RBC) −24%**.
			b) Control				EH 21	Results compare (a) *vs* (b).
116	XS PG	Years 2–14	a) F40/240 or B 2.5/5 b) Control	+5.9%. Not all patients included.		*Muscle* −18.9%***	EH/CCF 25	Controls *n* = 25 undergoing minor surgery. Matched age/sex but not disease.
107	DB PG PC	2	a) Indapamide 2.5 b) Placebo	+1.2%	0		EH 15 EH 12	6 weeks washout. Results compared with P. Both groups −4.7% compared with basal.
108	DB PG PC	2	a) Cyclo 50–500 b) Placebo	0			EH 41 EH 12	No dose-related change Mg. LD. Results compare (a) *vs* (b).
140	OPEN PG	2	a) Burinex 0.5 + KCl b) F 20 + A 2.5	0			CCF 8 CCF 10	Results compared with basal and between groups. Previous therapy withdrawn 2 days.
114	XS PG	6+	a) HCh 25/100 b) Non-diuretic	+5.8%*		*MRT* +28.7%	EH 7 EH 8	Results compare (a) *vs* (b). No placebo group. Group matched for age, sex, but not weight. Diuretics stopped 2 days before MRT.
112	DB PG	12	a) HCh 72 b) Spiro 144	a) −8.1% b) −1.2%	*RBC* a) −25% b) 0	*Urine* a) −5.8% b) −3.1%	EH 9 EH 9	Results compared with basal. 4 weeks P pre-randomisation washout; no longterm P.
117	XS	6+	a) F80[a] b) Frumil c) Control	a) −7% b) +2%	*WBC* a) +12% b) +33%*** IC free Mg		CCF 10 CCF 12	[a] = 'or equivalent'. Controls = 22 normals. CCF groups matched for age/sex/other treatment. Results compared with controls.

Table 2 (*continued*)

Reference	*Type of study*	*Time (months)*	*Drug*	*Serum or plasma*	*RBC or WBC*	*Other*	*Diagnosis number of patients*	*Comments*
					WBC	*ECG*		
110	DB PG	2	a) HCh 50 b) HCh 50 +TRI 100 c) CLT 50 d) Placebo	a) −1.2% b) +4.7%** c) −2.4% d) −2.4%	a) −2.2% b) +0.6% c) −6.4% d) −1.7%	No excess VES	EH 209	Results compared with basal. Other groups with added K and Mg—no differences noted. No excess arrhythmia.

of thiazide diuretic, Mg_{SM} was within normal limits on long-term therapy (58–240 months) but fell during the continued use of thiazide diuretic for a further 6 months. The authors attribute this fall to the patients not taking diuretic tablets regularly prior to the trial. Triamterene, amiloride and magnesium supplements increased Mg_{SM} by 14.6%, 6.4% and 12% respectively [128, 129, 130]. Mg_{heart} content was not affected by diuretic therapy in the studies of Reinhart *et al.* [44] and Ralston *et al.* [15, 46]. It has been suggested that the elderly are more likely to suffer Mg deficiency following diuretic therapy because of inadequate diet. However, Mg_S [118] and Mg_{SM} [134] concentrations may fall with age irrespective of diuretic therapy. Some surveys of elderly patients in a community [121] or following admission to hospital [135, 136] suggest a higher incidence of hypomagnesaemia in patients on diuretics. Caution is needed in interpreting these studies since patients were not matched for disease states. Hypomagnesaemia did not affect mortality or length of stay in hospital. These uncontrolled studies contain defects of design which include inappropriate control populations, historical controls, retrospective analysis, the use of a laboratory range, insufficient published data, inaccurate methodology and findings that were a side issue to the main aim of the study.

References

1 Ramsay LE. Diuretic drugs, Chapter 22: pp. 185–198. In *Side effect of drugs*, Annual 10. Ed Dukes MNG. 1986; Amsterdam: Elsevier Science Publishers, B.V.

2 Swales JHD. Magnesium deficiency and diuretics. *Br med J* 1982; **285**: 1377–1378.

3 Brenton DP, Gordon TE. Magnesium. *Br J hosp Med* 1984; **32**: 60–69.

4 Reinhart RA. Magnesium metabolism. A review with special reference to the relationship between intracellular content and serum levels. *Arch intern Med* 1988; **148**: 2415–2420.

5 Seelig M. Cardiovascular consequences of magnesium deficiency and loss: pathogenesis, prevalence and manifestations—magnesium and chloride loss in refractory potassium repletion. *Am J Cardiol* 1989; **63**: 4G–21G.

6 Hardwick LL, Jones MR, Brautbar N, Lee DB. Magnesium absorption: mechanisms and the influence of vitamin D, calcium and phosphate. *J Nutr* 1991; **121**: 13–23.

7 Wallach S. Availability of body magnesium during magnesium deficiency. *Magnesium* 1988; **7**: 262–270.

8 Quamme GA, Dirks JH. Magnesium homeostasis. Part 2: Renal handling of magnesium. In *Textbook of Nephrology*. Ed Massry SG, Glassnock RJ. Chapter 21, pp. 315–323 1989; Baltimore: Williams and Wilkins, 2nd edition.

9 Wittner M, Di Stefano A, Wangemann P, Greger R. How do loop diuretics act? *Drugs* 1991; **41** (Suppl. 3): 1–13.

10 De Rouffignac C, Di Stefano A, Wittner M, Roinel N, Elalouf JM. Consequences of differential effects of ADH and other peptide hormones on thick ascending limb of mammalian kidney. *Am J Physiol* 1991; **260**: R1023–R1035.

11 Garfinkel D, Garfinkel L. Magnesium and regulation of carbohydrate metabolism at the molecular level. *Magnesium* 1988; **7**: 249–261.

12 Reinhart RA. Clinical correlates of the molecular and cellular actions of magnesium on the cardiovascular system. *Am Heart J* 1991; **121**: 1513–1521.

13 White RE, Hartzell HC. Magnesium ions in cardiac function. *Biochem Pharmac* 1989; **38**: 859–867.

14 Surawicz B. Is hypomagnesaemia or magnesium deficiency arrhythmogenic? *J Am Coll Cardiol* 1989; **14**: 1093–1096.

15 Ralston MA, Murnane MR, Unverferth DV, Leier CV. Serum and tissue magnesium concentrations in patients with heart failure and serious ventricular arrhythmias. *Ann int Med* 1990; **113**: 841–846.

16 Editorial. Magnesium for acute myocardial infarction. *Lancet*, 1991; **338**: 667–668.

17 Woods KL. Possible pharmacological actions of magnesium in acute myocardial infarction. *Br J clin Pharmac* 1991; **32**: 3–10.

18 Teo K, Yusuf S, Collins R, Held PH, Peto R. Effects of intravenous magnesium in suspected acute myocardial infarction: overview of randomised trials. *Br med J* 1991; **303**: 1499–1503.

19 Murphy E, Freudenrich CC, Lieberman M. Cellular magnesium and Na/Mg exchange in heart cells. *Ann Rev Physiol* 1991; **53**: 273–287.

20 Young IS, Goh EML, McKillop UH, Stanford CF, Nicholls DP, Trimble ER. Magnesium status and digoxin toxicity. *Br J clin Pharmac* 1991; **32**: 717–721.

21 Whyte KF, Whitesmith R, Reid JL. The effect of diuretic therapy on adrenaline-induced hypokalaemia and hypomagnesaemia. *Eur J clin Pharmac* 1987; **34**: 333–337.

22 Joborn H, Akerstrom G, Ljunghall S. Effects of exogenous catecholamines and exercise on plasma magnesium concentrations. *Clin Endocr* 1985; **23**: 219–226.

23 Rasmussen HS. Clinical intervention studies on magnesium in myocardial infarction. *Magnesium* 1989; **8**: 316–325.

24 Abraham AS, Rosenman D, Meshulam Z, Zion M, Eylath U. Serum, lymphocyte, erythrocyte potassium, magnesium and calcium concentrations and their relationship to tachyarrhythmias in patients with acute myocardial infarction. *Am J Med* 1986; **81**: 983–988.

25 Paolisso G, Scheen A, D'Onofrio F, Lefebvre P. Magnesium and glucose homeostasis. *Diabetologica* 1990; **33**: 511–514.

26 Fletcher GF, Sweeney ME, Fletcher BJ. Blood magnesium and potassium alterations with maximal treadmill exercise testing: effects of β-adrenergic blockade. *Am Heart J* 1990; **121**: 105–110.

27 Quamme GA. Renal handling of magnesium: Drug and hormone interactions. *Magnesium* 1986; **5**: 248–272.

28 Bremme K, Eneroth P, Nordstrom L, Nilsson B. Effects of infusion of the beta-adrenoceptor agonist Terbutaline on serum magnesium in pregnant women. *Magnesium* 1986; **5**: 85–94.

29 Elin RJ, Hosseini JM, Fitzpatrick L, Bliziotes MM, Marx SJ. Blood magnesium status of patients with parathyroid disease. *Magnes Trace Elem* 1990; **9**: 119–123.

30 Ginsburg S, Smith JG, Ginsburg FM, Reardon JZ, Aikawa JK. Magnesium metabolism of human and rabbit erythrocytes. *Blood* 1962; **20**: 722–729.

31 Watson WS, Hilditch TE, Horton PW, Davies DL, Lindsay R. Magnesium metabolism in blood and the whole body in man using ^{28}Magnesium. *Metabolism* 1979; **28**: 90–95.

32 Gonzalez-Serratos H, Rasgado-Flores H. Extracellular magnesium-dependent sodium efflux in squid giant axons. *Am J Physiol* 1990; **259**: C541–C548.

33 Flatman PW. The control of red cell magnesium. *Magnes Res* 1988; **1**: 5–11.

34 Flatman PW. Mechanisms of magnesium transport. *Ann Rev Physiol* 1991; **53**: 259–271.

35 Quamme GA, Dai LJ. Presence of a novel influx pathway for Mg^{2+} in MDCK cells. *Am J Physiol* 1990; **259**: C521–C525.

36 Grubbs RD. Effect of epidermal growth factor on magnesium homeostasis in BC_3H_1 myocytes. *Am J Physiol* 1991; **260**: C1158–C1164.

37 Romani A, Scarpa S. Regulation of cell magnesium. *Arch Bio Bioph* 1992; **298**: 1–12.

38 Wills MR, Sunderman FW, Savory J. Methods for the estimation of serum magnesium in clinical laboratories. *Magnesium* 1986; **5**: 317–327.

39 Kuller L, Farrier N, Caggiula A, Borhani N, Dunkle S. Relationship of diuretic therapy and serum magnesium levels among participants in the Multiple Risk Factor Intervention Trial. *Am J Epidemiol* 1985; **122**: 1045–1059.

40 Gonzales-Revalderia J, Garcia-Bermejo S, Menchen-Herreros A, Fernandez-Rodriguez E. Biological variation of Zn, Cn and Mg in serum of healthy subjects. *Clin Chem* 1990; **36**: 2140–2141.

41 Gallacher RE, Browning MCK, Fraser CG, Wilkinson SP, MacLennan WJ. A method for simultaneously determining plasma, erythrocyte and leukocyte sodium, potassium and magnesium: reference values and considerations from biological variation data. *Clin Chem* 1987; **33**: 1326–1330.

42 Elin RJ, Hosseini JM, Ruddel M. Intra-individual variability of blood magnesium. *Clin Chem* 1989; **35**: 1114–1115.

43 Sjogren A, Floren CH, Nilsson A. Magnesium and potassium status in healthy subjects as assessed by analysis of magnesium and potassium in skeletal muscle biopsies and magnesium in mononuclear cells. *Magnesium* 1987; **6**: 91–99.

44 Elin RJ. Status of the determination of the magnesium in mononuclear blood cells in humans. *Magnesium* 1988; **7**: 300–305.

45 Reinhart RA, Marx JJ, Broste SK, Haas RG. Myocardial magnesium: relation to laboratory and clinical variables in patients undergoing cardiac surgery. *J Am Coll Cardiol* 1991; **17**: 651–656.

46 Ralston MA, Murnane MR, Kelley RE, Altschuld RA. Magnesium content of serum, circulating mononuclear cells, skeletal muscle and myocardium in congestive heart failure. *Circulation* 1989; **80**: 573–580.

47 Wong NLM, Sutton RAL, Dirks JH. Is lymphocyte magnesium concentration a reflection of intracellular magnesium concentration. *J lab clin Med* 1988; **112**: 721–726.

48 Alvarez-Leefmans FJ, Giraldez F, Gamino SM. Intracellular free magnesium in excitable cells: its measurement and its biologic significance. *Can J Physiol Pharmac* 1987; **65**: 915–925.

49 Rotevatn S, Sarheim H, Murphy E. Intracellular free magnesium concentration: relevance to cardiovascular medicine. *Acta Physiol Scand* 1991; **599** (Suppl.): 125–133.

50 London RE. Methods for measurement of intracellular magnesium: NMR and fluorescence. *Ann Rev Physiol* 1991; **53**: 241–258.

51 Ng LL, Davies JE, Garrido MC. Intracellular free magnesium in human lymphocytes and the response to lectins. *Clin Sci* 1991; **80**: 539–547.

52 Thoren L. Magnesium deficiency in gastrointestinal fluid loss. *Acta chir scand* 1963; **306** (Suppl.) 5–65.

53 Caddell JL, Reed GF. Validity of the parenteral magnesium load test for mature mammals. *Magnesium* 1989; **8**: 65–70.

54 Avioli LV, Berman M. ^{28}Mg kinetics in man. *J appl Physiol* 1966; **21**: 1688–1694.

55 Aikawa JK, Gordon GS, Rhoades EL. Magnesium metabolism in human beings: Studies with ^{28}Mg. *J appl Physiol* 1960; **15**: 503–507.

56 Lowney P, Stern JS, Gershwin E, Keen CL. Magnesium deficiency and blood 2,3-diphosphoglycerate concentrations in sedentary and exercised male Osborne-Mendel rats. *Metabolism* 1990; **39**: 837–841.

57 Brilla LR, Fredrickson JH, Lombardi VP. Effect of hypomagnesaemia and exercise on slowly exchanging pools of magnesium. *Metabolism* 1989; **38**: 797–800.

58 Farkas RA, McAllister CT, Blachley JD. Effect of magnesium salt anions on potassium balance in normal and magnesium-depleted rats. *J lab clin Med* 1987; **110**: 412–417.

59 Kjeldsen K, Norgaard A. Effect of magnesium depletion on ^{3}H-ouabain binding site concentration in rat skeletal muscle. *Magnesium* 1987; **6**: 55–60.

60 Geven WB, Vogels-Mentink GM, Willems JL, Joordens JJM, Hilbers CW, Monnens LAH. Experimental magnesium depletion in the dog: relation between total and ultrafiltrable Mg in plasma and total and ionized Mg in erythrocytes. *Magnes Bull* 1990; **12**: 166–169.

61 Fry CH. Measurement and control of intracellular magnesium ion concentration in guinea pig and ferret ventricular myocardium. *Magnesium* 1986; **5**: 306–316.

62 Sutton RAL. Hypomagnesaemia and magnesium deficiency. *J Roy Coll Phys Lond* 1968; **2**: 358–370.

63 Fitzgerald MG, Fourman P. An experimental study of magnesium deficiency in man. *Clin Sci* 1956; **15**: 635–647.

64 Ryan MP. Magnesium and potassium-sparing diuretics. *Magnesium* 1986: **5**: 282–292.

65 Ryan MF. The role of magnesium in clinical biochemistry: an overview. *Ann clin Biochem* 1991; **28**: 19–26.

66 Fatemi S, Ryzen E, Flores J, Endres DB, Rude RK. Effect of experimental human magnesium depletion on parathyroid hormone secretion and 1,25 dihydroxyvitamin D metabolism. *J clin Endocrinol Metab* 1991; **73**: 1067–1072.

67 Grubbs RD, Maguire ME. Magnesium as a regulatory cation: criteria and evaluation. *Magnesium* 1987; **6**: 113–127.

68 Gunther T. Functional compartmentation of intracellular magnesium. *Magnesium* 1986; **5**: 53–59.

69 Field MJ, Chrisp JS, Lawrence JR. Magnesium excretion during brisk diuresis in rats: dependence on diuretic mechanism. In *Diuretics III: Chemistry, pharmacology and clinical applications*, pp. 101–103. Eds Puschett JB, Greenberg A. 1990; Amsterdam: Elsevier Science Publishing Co., Inc.

70 Poutsiaka JW, Madissoo H, Millstein LG, Kirpan J. Effects of benzydroflumethiazide (Naturetin) on the renal excretion of calcium and magnesium by dogs. *Tox appl Pharmac* 1961; **3**: 455–458.

71 Borchgrevink PC, Jynge P. Prolonged diuretic administration and myocardial tolerance to ischaemia. *Pharmac Tox* 1987a; **61**: 254–259.

72 Borchgrevink PC, Holten T, Jynge P. Tissue electrolyte changes induced by high doses of diuretics in rats. *Pharmac Tox* 1987b; **60**: 77–80.

73 Adam WR, Craik DJ, Kneen M, Wellard RM. Effect of magnesium depletion and potassium depletion and chlorothiazide on intracellular pH in the rat, studied by 31^P NMR. *Clin exp Pharmac Physiol* 1989; **16**: 33–40.

74 Alexander BS. Diuretic-induced CNS magnesium alteration and digoxin intoxication. *Magnesium* 1988; **7**: 210–218.

75 Rabkin SW, Roob O. Effect of chronic diuretics on epinephrine-induced ventricular arrhythmias: a comparison of hydrochlorothiazide and amiloride in the rat. *J cardiovasc Pharmac* 1987; **10**: 238–245.

76 Wallach S. Effects of magnesium on skeletal metabolism. *Magnes Trace Elem* 1990; **9**: 1–14.

77 Reyes AJ. Effect of diuretics on outputs and flows of urine and urinary solutes in healthy subjects. *Drugs* 1991; **41** (Suppl. 3): 35–59.

78 Leary WP, Reyes AJ, Van der Byl KV, Acosta-Barrios TN. Effects of captopril hydrochlorothiazide and their combination on timed urinary excretions of water and solutes. *J cardiovasc Pharmac* 1985; **7**: S56–S62.

79 Leary WP, Reyes AJ, Wynne RD, Van der Byl K. Renal excretory actions of frusemide of hydrochlorothiazide and of the vasodilator flosequinan in healthy subjects. *J int med Res* 1990; **18**: 120–141.

80 Leary WP, Reyes AJ. Diuretic-induced magnesium losses. *Drugs* 1984; **28** (Suppl. 1): 182–187.

81 Davies DL, Lant AF, Millard NR, Smith AJ, Ward JW, Wilson GM. Renal action, therapeutic use, and pharmacokinetics of the diuretic bumetanide. *Clin Pharmac Ther* 1974; **15**: 141–155.

82 Warrington SJ, Sinclair AJ, Johnston A. Effects of single doses of a 20 mg frusemide/2.5 mg amiloride combination, 20 mg frusemide and placebo on plasma and urine electrolytes in healthy men. *J int med Res* 1990; **18** (Suppl. 2): 3B–9B.

83 Labeeuw M, Pozet N, Zech P, Hadj-Aissa A, Sassard J. Magnesuria induced by thiazides and the influence of triamterene. *Fundam clin Pharmac* 1987; **1**: 225–232.

84 Kiil F. Permutation trial of diuretics chlorothiazide and hydroflumethiazide. *Circulation* 1960; **21**: 717–723.

85 Knauf H, Reuter K, Mutschler E. Limitation on the use of amiloride in early renal failure. *Eur J clin Pharmac* 1985; **28**: 61–66.

86 Van Meyel JJM, Smits P, Gribnau FWJ. Absence of magnesium sparing effect of a single dose of triamterene in combination with frusemide in healthy male adults. *Br J clin Pharmac* 1990; **30**: 774–777.

87 Jorgensen FS, Transbol I. The effects of bendroflumethiazide on the renal handling of calcium, magnesium and phosphate in normocalcemic renal stone formers and in hyperparathyroidism. *Acta med scand* 1973; **194**: 327–334.

88 Parfitt AM. The interactions of thiazide diuretics with parathyroid hormone and vit. D. Studies in patients with hypoparathyroidism. *J clin Invest* 1972; **51**: 1879–1888.

89 Sullivan JM, Dluhy RG, Wacker WEC, Solomon HS, Williams GH, Samaha JK. Inter-relationships among thiazide diuretics and calcium, magnesium, sodium and potassium balance in normal and hypertensive man. *J clin Pharmac* 1978; **18**: 530–543.

90 Bergstrom J, Hultman E, Solheim SB. The effect of mefruside on plasma and muscle electrolytes and blood pressure in normal subjects and in patients with essential hypertension. *Acta med scand* 1973; **194**: 427–432.

91 McInnes GT, Davies DL. Plasma and RBC electrolytes following hydrochlorothiazide and potassium sparing agents. In *Diuretics II. Chemistry, pharmacology and clinical applications*, pp 729–731. Eds Puschett JB, Greenberg A. 1987; Amsterdam: Elsevier Science Publishing Co., Inc.

92 Lipworth BJ, McDevitt DG, Balfour DJK, Struthers AD. Prior treatment with diuretic augments the hypokalaemic and electrocardiographic effects of inhaled salbutamol in man. *Clin Sci* 1989; **76** (Suppl. 20): 30P.

93 Ryan MP, Ryan MF, Counihan TB. The effect of diuretics on lymphocyte magnesium and potassium. *Acta med scand* 1981; **647** (Suppl): 153–161.

94 Bergstrom J, Friden AM. The effect of hydrochlorothiazide and amiloride administered together on muscle electrolytes in normal subjects. *Acta med scand* 1975; **197**: 415–419.

95 Pak CYC. Hydrochlorothiazide therapy in nephrolithiasis: effect on the urinary activity product and formation of brushite. *Clin Pharmac Ther* 1973; **14**: 209–217.

96 Goldenberg K, Wergowske G, Chatterjee S, Kezdi P. Effects of thiazide on erythrocyte sodium and potassium concentrations and Na^+K^+ATPase in hypertensive patients. *Clin exp Hypertension* 1988; A **10**: 91–103.

97 Ramsay F, Crawford RJ, Allman S, Bailey R, Martin A. An open comparative study of two diuretic combinations, frusemide/amiloride (Frumil) and bumetanide/potassium chloride (Burinex K), in the treatment of congestive cardiac failure in hospital out-patients. *Curr med Res Opin* 1988; **10**: 682–689.

98 Kisters K, Zidek W, Rahn KH. Action of trichlormethiazide and amiloride on cellular Na^+, K^+ and Mg^+ concentrations. *Schweiz med Wschr* 1989; **119**: 1837–1839.

99 Barnes JN, Drew PJT, Skehan JD, Vandenburg MJ. Diuretic associated hypomagnesaemia. *Br med J* 1983; **286**: 146–147.

100 Kohvakka A, Heinonen L, Pietinen P, Salo H, Eisalo A. Potassium and magnesium balance in thiazide-treated cardiac patients with special reference to diet. *Acta med scand* 1982; **668** (Suppl.): 102–109.

101 Sundberg S, Salo H, Gordin A, Melamies L. Lamminisivu U, Nuotto E, Keranen A. Effect of low dose diuretics on plasma and blood cell electrolytes, plasma uric acid and blood glucose. *Acta med scand* 1982; **668** (Suppl.): 95–101.

102 Papademetriou V, Notargiacomo A, Heine D, Fletcher RD, Fries ED. Effects of diuretic therapy and exercise-related arrhythmias in systemic hypertension. *Am J Cardiol* 1989; **64**: 1152–1156.

103 Fehske KJ, Kisters K, Kwapisz A, Zidek W. Cellular magnesium handling during treatment with piretanide. In *Diuretics III. Chemistry, pharmacology and clinical applications*, pp. 770–775. Eds Puschett JB, Greenberg A. 1990; Amsterdam: Elsevier Science Publishing Co.

104 Nederfors T, Twetman S, Dahlof C. Effects of the thiazide diuretic bendroflumethiazide on salivary flow rate and composition. *Scand J Dent Res* 1989; **97**: 520–527.

105 Araoye MA, Khatri IM, Yao LL, Freis ED. Leukocyte

intracellular cations in hypertension: effect of antihypertensive drugs. *Am Heart J* 1978; **96**: 731–738.
106 Zemel MB, Zemel PC, Bijlani S, Bedford-Johnson BA, Sowers JR. Relative effects of maxzide and hydrochlorothiazide on erythrocyte cations and forearm vascular resistance. In *Diuretics III: Chemistry, pharmacology and clinical applications*, pp 495–497. Eds Puschett JB, Greenberg A. 1990; Amsterdam: Elsevier Science Publishing Co., Inc.
107 Taylor DR, Constable J, Sonnekus M, Milne FJ. Effect of indapamide on serum and red cell cations, with and without magnesium supplementation, in subjects with mild hypertension. *S Afr med J* 1988; **74**: 273–276.
108 McVeigh G, Galloway D, Johnston D. The case for low dose diuretics in hypertension: comparison of low and conventional doses of cyclopenthiazide. *Br med J* 1988; **297**: 95–98.
109 Laerum E. Metabolic effects of thiazide versus placebo in patients under long-term treatment for recurrent urolithiasis. *Scand J Urol Nephrol* 1984; **18**: 143–149.
110 Siegel D, Hulley SB, Black DM, Cheitlin MD, Sebastian A, Seeley DG, Hearst N, Fine R. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *J Am med Ass* 1992; **267**: 1083–1089.
111 Hattori K, Saito K, Sano H, Fukuzaki H. Intracellular magnesium deficiency and effect of oral magnesium on blood pressure and red cell sodium transport in diuretic-treated hypertensive patients. *Jap Circ J* 1988; **52**: 1249–1256.
112 Garcia-Puig J, Miranda ME, Mateos F, Herrero E, Lavilla P, Gill A. Hydrochlorothiazide versus spironolactone: long-term metabolic modifications in patients with essential hypertension. *J clin Pharmac* 1991; **31**: 455–461.
113 Cocco G, Iselin HU, Strozzi C, Cesana B, Baumeler HR. Magnesium depletion in patients on long-term chlorothiazide therapy for essential hypertension. *Eur J clin Pharmac* 1987; **32**: 335–338.
114 Seelig CB. Magnesium deficiency in two hypertensive patient groups. *S med J* 1990; **83**: 739–742.
115 Abraham AS, Rosenman D, Meshulam Z, Balkin J, Zion M, Eylath U. Intracellular cations and diuretic therapy following acute myocardial infarction. *Arch intern Med* 1986; **146**: 1301–1303.
116 Dorup I, Skajaa K, Clausen T, Kjeldsen K. Reduced concentrations of potassium, magnesium, and sodium-potassium pumps in human skeletal muscle during treatment with diuretics. *Br med J* 1988; **296**: 455–458.
117 Ng LL, Garrido MC, Davies JE, Brochwicz-Lewinski MJ, Tan LB. Intracellular free magnesium in lymphocytes from patients with congestive heart failure treated with loop diuretics with and without amiloride. *Br J clin Pharmac* 1992; **33**: 329–332.
118 Hollifield JW. Magnesium depletion, diuretics and arrhythmias. *Am J Med* 1987; **82** (Suppl. 3A): 30–37.
119 Ahlstrand C, Tiselius H-G, Larsson L, Hellgren E. Clinical experience with long-term bendroflumethiazide treatment in calcium oxalate stone formers. *Br J Urol* 1984; **56**: 255–262.
120 Kroenke K, Wood DR, Hanley JF. The value of serum magnesium determination in hypertensive patients receiving diuretics. *Arch intern Med* 1987; **147**: 1553–1556.
121 Petri M, Cumber P, Grimes L, Treby D, Bryant R, Rawlins D, Ising H. The metabolic effects of thiazide therapy in the elderly: a population study. *Age and Ageing* 1986; **15**: 151–156.
122 Abraham AS, Meshulam Z, Rosenmann D, Eylath U. Influence of chronic diuretic therapy on serum, lymphocyte and erythrocyte potassium, magnesium and calcium concentrations. *Cardiology* 1988; **75**: 17–23.
123 Cohen L, Kitzes R, Shnaider H. The myth of long-term thiazide-induced magnesium deficiency. *Magnesium* 1985; **4**: 176–181.
124 Halawa B. Hypotensive and metabolic effects of small doses of hydrochlorothiazide in the long-term treatment of elderly patients with systolic arterial hypertension. *Wiad lek* 1989; **42**: 210–217.
125 Seller RH, Ramirez-Muxo O, Brest AN, Moyer JH. Magnesium metabolism in hypertension. *J Am med Ass* 1965; **191**: 654–656.
126 Seller RH, Brest AN, Moyer JH. Serum and erythrocytic magnesium levels in congestive heart failure. Effect of hydrochlorothiazide. *Am J Cardiol* 1966; **17**: 786–797.
127 Schwinger RH, Antoni DH. Magnesium and potassium content in patients with heart failure and in healthy persons. Determination in lymphocytes, erythrocytes and plasma. *Z Kardiol* 1990; **79**: 735–741.
128 Dyckner T, Wester PO. Plasma and skeletal muscle electrolytes in patients on long-term diuretic therapy for arterial hypertension and/or congestive heart failure. *Acta med scand* 1987; **222**: 231–236.
129 Camara EJ, Cruz TR, Nassri JM, Rodrigues LE. Muscle magnesium content and cardiac arrhythmias during treatment of congestive heart failure due to chronic chagasic cardiomyopathy. *Braz J med Biol Res* 1986; **19**: 49–58.
130 Widmann L, Dyckner T, Wester P-O. Effects of triamterene on serum and skeletal muscle electrolytes in diuretic-treated patients. *Eur J clin Pharmac* 1988; **33**: 577–579.
131 Dyckner T, Wester PO, Widman L. Amiloride prevents thiazide-induced intracellular potassium and magnesium losses. *Acta med scand* 1988; **224**: 25–30.
132 Dyckner T, Wester PO, Widman L. Effects of peroral magnesium on plasma and skeletal muscle electrolytes in patients on long-term diuretic therapy. *Int J Cardiol* 1988; **19**: 81–87.
133 Ljunghall S, Backman U, Danielson B, Fellstrom B, Johansson G, Wikstrom B. Calcium and magnesium metabolism during long-term treatment with thiazides. *Scand J Urol Nephrol* 1981; **15**: 257–262.
134 Forsberg AM, Nilsson E, Werneman J, Bergstrom J, Hultman E. Muscle composition in relation to age and sex. *Clin Sci* 1991; **81**: 249–256.
135 Martin BJ, Black J, McClelland AS. Hypomagnesaemia in elderly hospital admissions: a study of clinical significance. *Q J Med* 1991; **78**: 177–184.
136 Thomas AJ, Hodkinson HM. Which diuretics cause hypomagnesaemia? A study of elderly in-patients. *J clin exp Gerontology* 1981; **3**: 269–283.
137 Leary WP, Reyes AJ, Van der Byl K. Effects of hydrochlorothiazide and amiloride combination on plasma magnesium in patients with essential hypertension. *Magnes Bull* 1984; **4**: 127–132.
138 Stewart DE, Ikram H, Espiner EA, Nicholls MG. Arrhythmogenic potential of diuretic induced hypokalaemia in patients with mild hypertension and ischaemic heart disease. *Br Heart J* 1985; **54**: 290–297.
139 Verho M, Irmisch R, De Looze S, Rangoonwala B. Lack of effect of piretanide (a potassium stable diuretic) on serum magnesium. *Int J clin Pharmac Res* 1987; **7**: 433–442.
140 Latta D, Finnamore VP, Dalton K, Allman S. An open, randomized comparative study of low-strength Frusemide/Amiloride combination and bumetanide/potassium chloride in the treatment of mild congestive cardiac failure. *J int med Res* 1990; **18** (Suppl. 2): 10B–16B.

(Received 24 September 1992, accepted 2 March 1993)